Remarks/Arguments

Favorable reconsideration of the application is respectfully requested in view of the following remarks.

Claims 7-13 are pending in the application. Claims 7-13 have been rejected.

Claims 7-13 have been rejected under 35 U.S.C. §103(a) as being unpatentable over EP0613687A1 (Deckers et al.) in view of U.S. Patent 6,262,098B1(Huebner et al.) and further in view of EP0389035B1 (Sas et al.). In particular, the Examiner stated:

> "Deckers et al. teach a method of treating breast cancer with tibolone without undesirable side effects associated with estrogen (pg. 2, lines 6-41). The daily dosage for tibolone is 0.003 to 3.0 mg per kg body weight, which for the average individual weighing 70 kg is 0.21 to 210 mg daily dosage (pg. 2, lines 51-53).
>
> However, Deckers et al. fail to disclose aromatase inhibitors and the estrogen-related complaints.
>
> Huebner et al. teach that aromatase inhibitors, such as exemestane, aminoglusthimide, letrozole, and anastrozole (col. 34, lines 24-45) can be used for treating estrogen receptor-mediated disorders including osteoporosis and breast cancer (col. 13, lines 38-50)
>
> Sas et al. teach that tibolone (pg. 2, lines 5-15) is useful for treating menopausal complaints (climacteric) and osteoporosis (bone loss) (page 2, lines 51-52).
>
> Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to combine the treatments of osteoporosis and breast cancer by administering tibolone during or after administration of aromatase inhibitors.
>
> A person of ordinary skill in the art would have been motivated to administer[ing] tibolone during or after administration of aromatase inhibitors for the treatment of osteoporosis and breast cancer because (1) both are taught to treat estrogen-deficient disorders such as osteoporosis; (2) both are taught to treat breast cancer; and (3) tibolone has the added benefit of reducing undesirable side effects, such as menopausal complaints, in treating estrogen-deficient disorders. A person of ordinary skill in the art would have been motivated to treat estrogen-deficient complaints in females with tibolone during or after administration of aromatase inhibitors because of the reasonable expectancy of successfully treating the disorder without the common side effects associated with estrogen-deficiency."

Applicants respectfully disagree with the Examiner's conclusion and submit that the combination of references does not make obvious claims 7-13 for the reasons stated below. Before addressing the rejection a brief summary of the present invention is provided.

The present invention as defined in claim 7 is directed to a method of treatment of estrogen-deficiency related complaints in female patients that exhibit these complaints while the female patients are on treatment with a drug which prevents the synthesis of endogenous estrogen. The method comprises administering to the patients an effective amount of tibolone. Accordingly, the invention is directed to a subgroup of female patients that exhibit estrogen-deficiency related complaints while being treated with a drug which prevents the synthesis of endogenous estrogen such as aromatase inhibitors. While postmenopausal women and women that are treated for cancer with SERMs (selective estrogen receptor modulators) have circulating estrogen, females on treatment with drugs that prevent estrogen from being synthesized lack circulating estrogen. Accordingly, in view of the lack of circulating estrogen, this subgroup of female patients can run an even higher chance and/or higher severity of estrogen-deficiency related complaints compared with postmenopausal females or females treated with SERMS. Thus, it presents a greater challenge to treat the complaints of this subgroup than in the case of either postmenopausal women or women on SERM treatment. That treatment with tibolone is effective in this subgroup of patients possessing estrogen-deficiency complaints related to a near total lack of circulating estrogen is nonobvious since tibolone itself hardly has an estrogenic activity, and is metabolized to compounds which have an approximately fifty-fold lower estrogenic receptor activity than estrogen (see specification on page 2, lines 20-23).

With respect to Deckers et al., while this reference describes use of tibolone to treat cancer there is no teaching or specific suggestion to utilize tibolone to treat estrogen-deficient complaints in a subgroup of female patients while the patients are being treated with a drug that prevents the synthesis of endogenous estrogen.

Heubner et al. is directed to isoxazole compounds that can act as estrogen receptor agonists or antagonists. The isoxazole compounds are described in Heubner et al. as being useful to treat the serious health problems caused by a failure to produce estrogen, such as osteoporosis, increased atherosclerotic deposits, and fluctuations in body temperature (see Heubner et al. column 1, lines 40-67-column 2, lines1-67, and columns 3-4). There is no teaching or specific suggestion in Heubner et al. that tibolone can be administered to treat estrogen-deficiency related complaints in female patients while the patients are on treatment with a drug that prevents endogenous synthesis of estrogen, nor is there any teaching or specific suggestion that the isoxazole compounds can be substituted with tibolone to treat a subgroup of female patients while the patients are on treatment with a drug that inhibits endogenous synthesis of estrogen.

The Examiner contends in part that Heubner et al. teach that aromatase inhibitors can be used to treat estrogen receptor-mediated disorders including osteoporosis. The Examiner also contends that one skilled in the art would be motivated to administer tibolone during or after

administration of aromatase inhibitors for the treatment of osteoporosis because both drugs are taught to treat estrogen-deficient disorders such as osteoporosis. Heubner et al., however, while indicating on column 34, lines 23-28, that the isoxazole compounds can be administered in combination with one or more other compounds as described therein, and/or in combination with other agents used in the treatment and/or prevention of estrogen receptor-mediated disorders, does not teach or specifically suggest that aromatase inhibitors can be used to treat osteoporosis. Indeed, aromatase inhibitors, in preventing synthesis of endogenous estrogen, and thus resulting in a near total lack of circulating estrogen, would be considered by one skilled in the art as a drug that would contribute to osteoporosis rather than a drug that would treat or prevent osteoporosis. Accordingly, in contrast to the Examiner's statements that one skilled in the art would be motivated to administer tibolone during or after administration of aromatase inhibitors for treatment for osteoporosis because both tibolone and aromatase inhibitors are taught to treat estrogen-deficient disorders such as osteoporosis, one skilled in the art would not consider that both aromatase inhibitors and tibolone could be used for the same purpose, i.e., to treat osteoporosis. Thus, one skilled in the art would not be motivated to use tibolone to treat estrogen-deficiency related complaints in such a subgroup of female patients.

Further, since aromatase inhibitors and tibolone would not be used for the same purpose of treating estrogen-deficient disorders, what other teaching or specific suggestion is provided in Huebner et al. that would motivate one skilled in the art to select aromatase inhibitors out of a laundry list of compounds (see Huebner et al., column 34, lines 30-67 to column 35, lines 1-35) to combine with tibolone to specifically treat estrogen-deficiency related complaints in a subgroup of female patients as recited in claim 7.

It is further submitted that the Examiner is relying upon hindsight to arrive at a determination of obviousness. It is well established that it is impermissible to use the claimed invention as an instruction manual or template to piece together the teachings of the prior art so that the claimed invention is rendered obvious. One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fritch*, quoting *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir.1988). In the present case, the Examiner has selected aromatase inhibitors from the multitude of drugs listed in Huebner et al. to combine with tibolone to treat estrogen-deficiency related complaints in a specific subgroup of female patients without any teaching, suggestion or motivation in Huebner et al. or Deckers et al. to make such a combination, and thus has used impermissible hindsight to arrive at the present invention.

With respect to Sas et al., while this reference teaches use of tibolone for treating menopausal complaints and for combating osteoporosis, there is no teaching or specific

suggestion in Sas et al. to use tibolone to treat estrogen-deficiency related complaints in a subgroup of female patients while the patients are on treatment with a drug such as an aromatase inhibitor which prevents the synthesis of endogenous estrogen. Further, there is no teaching or specific suggestion in Sas et al. that tibolone can be substituted for the isoxazole compounds of Heubner et al. to specifically treat estrogen-deficiency related complaints in female patients while they are on treatment with a drug that prevents synthesis of endogenous estrogen. Accordingly, the combination of Deckers et al., Huebner et al. and Sas et al. does not teach or specifically suggest the use of tibolone to treat estrogen-deficiency related complaints in a subgroup of female patients as defined in claim 7.

Thus, in view of the absence of a specific suggestion or motivation in the combined prior art leading to the use of tibolone to treat this subgroup of patients, Applicants submit that the Examiner erred in rejecting claims 7-13.

In view of the above, withdrawal of the rejection of claims 7-13 under 35 U.S.C. §103(a) is respectfully requested.

A good faith effort has been made to place the present application in condition for allowance. If the Examiner believes a telephone conference would be of value, he is requested to call the undersigned at the number listed below.

Respectfully submitted,

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